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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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DAVIS WRIGHT TREMAINE, LLP
2600 CENTURY SQUARE
1501 FOURTH AVENUE
SEATTLE, WA 98101-1688

EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/825,566	LAIRD ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *21-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 1-24 are pending in the instant application. Claims 1-20 are currently under consideration at this time. Claims 21-24 are withdrawn from consideration as being drawn to a non elected invention. The following objections and rejections are either newly applied (as necessitated by amendment) or are reiterated. Response to applicant's arguments follow, where appropriate. This action is FINAL.

2. This application contains claims 21-24 drawn to an invention nonelected with traverse in Paper No. 8/9/2004. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

3. The rejections made under 35 USC 102 at sections 9-11 and under 35 USC 103 at section 14, with regard to Hahnel, Chen I, and Chen II, of the previous office action are withdrawn in view of the amendments to claim 1.

Specification

4. The amendment filed 8/9/2004, to the sequence listing, is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The sequence listing has been amended to include the sequences of SEQ ID NOS: 66-76. Upon thorough review of the

specification, however, it has been determined that the specification does not provide support for the sequences of SEQ ID NOS 66-76 for the reasons which follow.

SEQ ID NO: 66 represents the MYOD1 genomic sequence of Genbank Accession number given in table II. However, sequences in Genbank can be changed. The objection with regard to SEQ ID NO: 66 could be overcome with a declaration stating that the sequence of SEQ ID NO: 66 is the sequence of the Genbank Accession number that was used at the time the invention was made, before the filing of the instant application or that of the provisional application.

SEQ ID NO: 67 corresponds to "CpG island portion of SEQ ID NO: 66". The response asserts that it finds support by the definition of CpG islands given at pages 7 and 8 of the specification as originally filed. The specification was thoroughly reviewed, however it was not found to provide support for the specific molecule of SEQ ID NO: 67. While the specification generally teaches what CpG islands are, and also states that they 1) have a frequency of CpG dinucleotides corresponding to an 'observed/expected' ratio >.6 and 2) have a GC content >.5, such teaching, it is clear from the definitions set forth at page 7 that these values are dependent on the length of the DNA fragment. The specification does not make clear how it would be determined what the cutoff points (ie: how long the fragments are) for the molecule were, how big the molecule was etc. For example, if the sequence of SEQ ID NO: 67 were truncated by one nucleotide on either end, would it still provide acceptable ratio and GC content? No indication is given in the specification, of any formula that could be used such that the only result for a CpG island 'portion' would be that of SEQ ID NO: 67. Accordingly, one of ordinary skill in the art reading the contents of the specification would not be immediately aware of the

specific sequence of SEQ ID NO: 67 given the disclosure in the specification at the time it was originally filed. Further, it does not appear that given the formulas in the specification, the only molecule that would result from the given accession number would be the specific molecule of SEQ ID NO: 67.

The response asserts further that SEQ ID NOS: 68-76 correspond to fully upmethylated, or downmethylated sense and antisense sequences corresponding to either the genomic 'CpG island portion' of SEQ ID NO: 67 (SEQ ID NOS 68-71) or the genomic treated (SEQ ID NO: 72) sequence of MYOD1 defined by the forward and reverse primers of SEQ ID NOS 7 and 8 (SEQ ID NOS 73-76). The response asserts that such sequences find support at page 20, line 12 through page 21, line 35 of the specification. The specification, however, only generally discusses bisulfite treatment, the use of primers in such analysis, and the case of either fully methylated or fully unmethylated *primers*. It is known in the art, and acknowledged by the specification, that genomic CpG islands are not necessarily fully up or down methylated, in diseases, or in general. The specification provides no support for fully upmethylated or downmethylated genomic MYOD1 sequences, and therefore does not provide support for the sequences of SEQ ID NOS: 68-71, or SEQ ID NOS: 73-76. With regard to SEQ ID NO: 72, the response asserts that it is "genomic MYOD1 sequence corresponding to treated DNA amplicon" defined by primers SEQ ID NO: 7 and 8. It is unclear how this sequence is different from SEQ ID NOS: 66, 67, or 73. A review of the specification, however, indicates that the specification provides no support for the specific sequence of SEQ ID NO: 72 or how this sequence is "treated".

Applicant is required to cancel the new matter in the reply to this Office Action.

Response to Arguments

5. The response asserts with regard to SEQ ID NO: 66 that applicants are obtaining signatures for a declaration. As no signatures have been provided, this objection is maintained.

The response asserts with regard to SEQ ID NO: 67 that applicant's originally filed disclosure teaches multiple species of a genus that is sufficiently described by an accession number and a definition for CpG islands and that all possible cut off points or end positions of CpG islands within SEQ ID NO: 67 are taught and disclosed by virtue of the accession number and the associated CpG formula. This argument has been thoroughly reviewed but was not found persuasive. Firstly, it is noted that reliance on the accession number at this time is insufficient as sequences in Genbank can be changed. Additionally, with regard to the CpG island formula, it is clear from the definitions set forth at page 7 that the values are dependent on the length of the DNA fragment. The specification does not make clear how it would be determined what the cutoff points (ie: how long the fragments are) for the molecule were. For example, if the sequence of SEQ ID NO: 67 were truncated by one nucleotide on either end, would it still provide acceptable ratio and GC content? No indication is given in the specification, of any formula that could be used such that the only result for a CpG island 'portion' would be that of SEQ ID NO: 67. It does not appear that given the formulas in the specification, the only molecule that would result from the given accession number would be the specific molecule of SEQ ID NO: 67. The response argues that the formula coupled with the accession number provides a teaching of multiple species. This argument is not found persuasive

because such disclosure is a general teaching of a genus where no specific member of the genus has been described. No specific species is taught, nor does the specification provide any indication as to the criticality of this particular fragment, nor does it specifically denote this species from the general description of an accession number and formula for CpG islands.

With regard to SEQ ID NOS 68-71, the response asserts that the specification fully supports the specific fully up- or fully down-methylated species of SEQ ID NO: 67 and references the specification at page 21. This argument as well as the specification have been thoroughly reviewed but were not found persuasive. The specification only generally discusses bisulfite treatment, the use of primers in such analysis, and the case of either fully methylated or fully unmethylated *primers*. It is known in the art, and acknowledged by the specification, that genomic CpG islands are not necessarily fully up or down methylated, in diseases, or in general. Therefore, the fact that MYOD1 genomic CpG islands are not necessarily fully up or down regulated is not irrelevant as asserted in the response, because the specification has provided no support for any specific fully up or down regulated CpG islands. From the disclosure in the specification, the skilled artisan would be taught that CpG islands in the MYOD1 gene can be methylated, however there could be no deduction of any specific CpG island, nor of any specific level of methylation because the specification is silent as to such. The specification at the time of filing had only provided very general teachings of methylation of the MYOD1 gene. No specific teaching of any particular methylated CpG island region had been disclosed. However, after the filing date, applicant's seek to provide information as to specific CpG islands as well as specific levels of methylation, which were not described by the specification as originally filed. A general disclosure that fully up or down methylated primers can be made, does not provide

support for a fully up or down methylated CpG island region amplified by those primers. The specification provides no support for fully upmethylated or downmethylated genomic CpG island MYOD1 sequences, and therefore does not provide support for the sequences of SEQ ID NOS: 68-71.

With regard to SEQ ID NO: 72, the response asserts that the specification at table II explicitly teaches the amplicon of SEQ ID NO: 72 by providing the amplicon end points and that the primers and probes disclosed teach that the amplicon is of bisulfite treated sequences. This argument has been thoroughly reviewed but was not found persuasive because the disclosure at page 30, table II of the specification does not teach the level of CpG methylation of the amplicon resulting from amplification with the disclosed primers. Such information is critical to be able to determine what the sequence of subsequent bisulfite treated DNA would be as it is known that bisulfite treatment changes the sequence of a particular DNA depending on which CpG sequences are methylated and which are not. Therefore, the degree of methylation will determine what the sequence of the subsequent DNA is. As the specification does not teach the level of DNA methylation or which sequences within the amplicon were methylated, the specification provides no support for the specific bisulfite treated resulting sequence of SEQ ID NO: 72. In the previous office action, the question was raised as to how SEQ ID NO: 72 is different from SEQ ID NOS: 66, 67, or 73. The response has not addressed this question. Does the sequence of SEQ ID NO: 72 represent a bisulfite treated DNA sequence from a fully upmethylated or partially methylated DNA sequence? For the reasons already made of record, the arguments with regard to SEQ ID NO: 73-76 are also not found persuasive.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

6. Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection. It is noted that the response has provided no support or disclosure in the specification for support for the instantly amended claims.

The claims have been amended to recite "an esophageal cancer related condition" and "at least one" genomic CpG sequence. Such amendments introduce new matter for the following reasons. While the claims as originally filed provided support for methods of diagnosing a "cancer related condition", the specification provides no support for the broad recitation of "esophageal cancer related condition". The specification provides support for Barrett's esophagous, also identified by Barrett's intestinal tissue, as well as esophageal dysplasia and esophageal metaplasia, however such does not represent support for the full genus of any "esophageal cancer related condition". For example, such conditions also encompass GERD (gastroesophageal reflux disease), Tylosis (A genetic disorder characterized by thickening of the palms and soles, white patches in the mouth, and a very high risk of esophageal cancer), Esophageal Achalasia (loss of peristalsis), and Esophageal webs (structural abnormalities), which are risk factors or diseases associated with esophageal cancer for which the specification provides no support or description. The disclosure of the Barrett's esophagous, esophageal dysplasia and esophageal metaplasia are not representative of the full scope of any 'esophageal

related condition". As such, the amendment introduces new matter into the instantly claimed invention.

Additionally, the claims have been broadly amended to recite "at least one" CpG sequence. Such encompass diagnosis or prognosis based on the methylation of a single CpG dinucleotide in the MYOD1 gene. The specification does not provide any description or teaching of a method of diagnosis or prognosis solely using the methylation status of *any* single CpG dinucleotide. The specification and claims as originally filed set forth methods which determine the methylation state of genomic "CpG sequences" (plural), but do not teach or describe methods solely using a single dinucleotide sequence. Accordingly, the amendment introduces new matter into the instantly claimed invention.

7. Amended claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing or prognosing esophageal cancer, esophageal dysplasia, esophageal metaplasia, or Barrett's intestinal tissue, in an esophageal tissue sample by detecting hypermethylation of CpG islands in the MYOD1 gene as compared to normal esophageal tissue does not reasonably provide enablement for diagnosis or prognosis of any esophageal cancer related condition by detecting any type of methylation such as hypermethylation, hypomethylation or normal methylation in 'at least one" CpG sequence in the MYOD1 gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. [It is noted that that as stated in the previous office action, the following methods are enabled based on the state of the art at the time the invention was made: a

method of diagnosing breast cancer in a breast tissue sample by detecting hypermethylation of CpG islands in the MYOD1 gene, colorectal carcinoma in a colorectal tissue sample by detecting hypermethylation of CpG islands in the MYOD1 gene, or Embryonal rhabdomyosarcoma in a muscle tissue by detecting partial methylation of CpG islands in the MYOD1 gene or Alveolar rhabdomyosarcoma in muscle tissue by detecting hypomethylation of CpG islands in the MYOD1].

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are now broadly drawn to diagnosis or prognosis of esophageal cancer or any esophageal cancer related condition by detecting any type of methylation such as hypermethylation, hypomethylation or normal methylation in at least one CpG sequence in the MYOD1 gene in an esophageal tissue sample. The claims encompass a method of making any diagnostic or prognostic prediction or determination of any esophageal cancer related condition based on any methylation status of a single CpG sequence in the MYOD1 gene.

The amount of direction or guidance and Presence and absence of working examples:

The specification teaches that CpG islands in the promoter region of the MYOD1 gene were hypermethylated in intestinal metaplasia tissue as compared to normal esophageal tissue (see page 36, lines 4-6). The specification teaches that increases in MYOD1 methylation were found in esophageal adenocarcinoma, Barrett's esophagus, and dysplasia (see Fig. 1). The specification further teaches that MYOD1 hypermethylation was correlated with increases in tumor stage (see Fig. 4, page 38). The specification is silent, however, to an association between methylation of MYOD1 and diagnosis or prognosis, even at least in part, "any" esophageal cancer related condition. Esophageal cancer related conditions include not only Barrett's esophagous, Barrett's intestinal metaplasia, and esophageal dysplasia, but also GERD (gastroesophageal reflux disease), Tylosis (A genetic disorder characterized by thickening of the palms and soles, white patches in the mouth, and a very high risk of esophageal cancer), Esophageal Achalasia (loss of peristalsis), celiac disease, Plummer-Vinson syndrome and Esophageal webs (structural abnormalities), which are risk factors or diseases associated with esophageal cancer. The specification is silent with regard to any association between methylation of even a single CpG dinucleotide in MYOD1, and the large number of diseases or disorders encompassed by *any* "esophageal cancer related condition. Further, the specification provides no predictable correlation that hypermethylation of the MYOD1 gene is associated, diagnostic, or prognostic for any esophageal cancer related condition based on an association between esophageal cancer and certain esophageal cancer related condition, such as Barrett's esophagous. A large number of distinct disorders are encompassed by "esophageal cancer related conditions", which are not necessarily predictive of ultimate Barrett's esophagous or

esophageal carcinoma. These disorders only represent a small subset of risk factors, and would not necessarily be associated with methylation differences in the MYOD1 gene as compared to "normal" esophageal tissue or esophageal tissue from subjects not suffering from any such disorder.

Additionally, the claims have been amended to encompass diagnosis or prognosis based on the methylation state of one genomic CpG sequence. Such recitation encompasses an association between the methylation status of a single CpG dinucleotide and diagnostic or prognostic significance. However, the specification teaches that aberrant hypermethylation in cancer cells often occurs at CpG islands (page 1). This finding, strongly corroborated by the teachings in the art, suggest that the methylation of a single CpG island would not be predictably diagnostic or prognostic of any disease or disorder, including esophageal cancer or any "esophageal cancer related condition". CpG islands represent stretches of genomic DNA with a certain GC content, as defined by the specification. The specification teaches, however, that CpG dinucleotides outside of an island are presumably normally methylated (see page 33, last line). Given that the specification provides an association between *hyper*methylation of CpG sequences within CpG islands of the MYOD1 gene, the specification provides no predictable correlation that the methylation status of any single CpG dinucleotide outside of a CpG island in the MYOD1 gene, would be diagnostic or prognostic of any disease, let alone esophageal cancer or any "esophageal cancer related condition". Further, the recitation of detection of methylation status of a single CpG dinucleotide is disclosed in context with a comparison to the methylation at a corresponding CpG dinucleotide in a normal control DNA sample (see page 14).

The state of the prior art and the predictability or unpredictability of the art:

The disclosure of the prior and post filing date art teach that conditions that are considered risk factors for esophageal carcinoma, do not necessarily indicate that a patient will necessarily develop esophageal cancer. For example, Kyrgidis (Kyrgidis et al; Journal of Surgical Research, vol. 125, pages 189-212, 2005) teaches that while Barrett's esophagus represents the most serious histological consequence of gastroesophageal reflux disease (GERD), it only develops in 5-10% of patients with GERD. Streitz (Streitz et al; Annals of Thoraci Surgery, vol. 59, pages 1604-1609, 1995) teaches that there is a wide range of reported cancer risks in achalasia patients, from zero to 33 times that of the normal population (see abstract). Thus, as exemplified by the teachings in the art, the recitation of any "esophageal cancer related condition" encompasses a large group of diseases and disorders, which are not necessarily predictive of eventual Barrett's esophagus, or esophageal cancer. The art is silent with regard to a predictable association between methylation status of MYOD1 and the broadly encompassed recitation of "esophageal cancer related condition".

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

Therefore, based on the limited guidance in the specification, and the unpredictability taught in the art, it would require undue experimentation for one of skill in the art to practice the invention as broadly as it is claimed. The skilled artisan would have to screen a large number of

patients with the many different types of "esophageal cancer related conditions" to determine whether normal methylation, hypermethylation, or hypomethylation was diagnostic or prognostic for any type of "esophageal cancer related condition". Additionally, the skilled artisan would have to perform an exhaustive analysis of CpG dinucleotides within the MYOD1 gene to determine if *any* CpG dinucleotide could be used for diagnostic or prognostic purposes. Based on the teachings of the art and the specification that methylation status of CpG islands is associated with cancer, and that specifically, CpG dinucleotides outside of CpG islands tend to be methylated, and that hypermethylation of CpG islands in the MYOD1 gene is associated with esophageal carcinoma, Barrett's esophagus, intestinal metaplasia, and esophageal dysplasia, the skilled artisan would be required to perform a large amount of unpredictable trial and error analysis to establish that *any* CpG dinucleotide would be diagnostic or prognostic of esophageal cancer or any "esophageal cancer related condition". Further, based on the unpredictability in the art and the lack of guidance in the specification with regard to diagnosis of any type of esophageal cancer related condition, it is clear that the skilled artisan would be required to perform additional unpredictable trial and error analysis to determine whether methylation status of MYOD1 could be used to diagnose or prognose *any* esophageal cancer related condition. It also is noted that the claims do not set forth any specific methylation alteration in the MYOD1 gene from an esophageal tissue sample. The claims merely set forth an invitation to experiment as they leave it up to the skilled artisan to determine if an increase or decrease in methylation of MYOD1 compared to methylation in a control subject is indicative of esophageal cancer or esophageal cancer related condition. While hypermethylation of CpG islands of promoters of some genes involved in cancer have been associated with esophageal cancer, the specification

has not set forth any predictable correlation that hypomethylation or hypermethylation of MYOD1 is indicative of esophageal cancer or any esophageal cancer related condition.

Based on the lack of guidance in the specification and the unpredictability taught in the art, undue experimentation would be required of the skilled artisan to practice the invention as broadly as it is claimed. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of any working examples other than for Barrett's esophagus - intestinal metaplasia, or esophageal dysplasia, or analysis of hypermethylated CpG dinucleotides in CpG islands, the unpredictable teachings in the art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

8. The response asserts that the examiner's concern's with regard to diagnosis or prognosis of any cancer using any tissue sample has been obviated with the amendments to claim 1. The amendments have been thoroughly reviewed but do not place the instant claims in condition for allowance, for the reasons newly made of record above with regard to claim amendments, as well as the issues raised in the previous office action and maintained above (eg: lack of predictable correlation between any methylation status of MYOD1 and diagnosis or prognosis, which were not addressed in applicant's response).

Claim Rejections - 35 USC § 102

9. Claims 1-3, 5-8, 10, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Iacopetta, as defined by Kyrgidis (Kyrgidis et al; Journal of Surgical Research, vol. 125, pages 189-212, 2005) (Iacopetta et al; Int. J. of Cancer, vol. 17, pages 429-432, 1997).

The recitation of "esophageal cancer related condition" has been broadly interpreted to encompass colorectal cancer, as taught by Kyrgidis. Kyrgidis teaches that an increased risk for colorectal cancer is found in patients with Barrett's esophagus and esophageal carcinoma, and vice versa (see printout, page 5, first full para).

With regard to claims 1 and 6, Iacopetta teaches that regional hypermethylation of the Myf-3 (MYOD1) gene is an early and widespread event in colorectal neoplasia (see page 432, last para). The method of Iacopetta involves obtaining tissue from a test tissue to be diagnosed (see page 429, col. 2, 2nd full para; colorectal tissue), performing a methylation assay using restriction enzymes and nucleic acid probes (see page 429-430 bridging para; probe to 3' downstream region of Myf-3) to determine the methylation state of genomic CpG sequence for Myf-3. Iacopetta teaches that hypermethylation of the Myf-3 gene is strongly associated with the development of benign and malignant colorectal tumors, therefore Iacopetta teaches "making a diagnostic or prognostic prediction of the cancer based at least in part on the methylation state of the genomic CpG sequences (see page 431, col. 1, first sentence of "Discussion").

With regard to claims 2, 5, 7, and 10: the CpG sequences analyzed by Iacopetta inherently 'correspond to CpG islands' which are 'associated' with sequences defined by SEQ ID NOS 7-9. It is noted that this recitation has been broadly interpreted to encompass the gene

which can be analyzed by the recited SEQ ID NOS in the claim. The claims do not require analysis with the specifically recited SEQ ID NOS:.

With regard to claims 3 and 8, the MYOD1 gene analyzed by Iacopetta is inherently "defined by the oligonucleotide primers and probes" of SEQ IDNOS 7-9. It is noted that this recitation has been broadly interpreted to encompass the gene which is can be analyzed by the recited SEQ ID NOS in the claim. The claims do not require analysis with the specifically recited SEQ ID NOS:.

With regard to claim 20, Iacopetta teaches detecting extensive hypermethylation in adenomas and malignant colorectal tumors (see page 431, para bridging cols 1 and 2).

Claim Rejections - 35 USC § 103

10. Claims 15-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iacopetta, as defined by Kyrgidis, in view of Huang (Huang et al; Human Molecular Genetics, vol. 8, pages 459-470, 1999).

Iacopetta teaches that regional hypermethylation of the Myf-3 (MYOD1) gene is an early and widespread event in colorectal neoplasia (see page 432, last para). The method of Iacopetta involves obtaining tissue from a test tissue to be diagnosed (see page 429, col. 2, 2nd full para; colorectal tissue), performing a methylation assay using restriction enzymes and nucleic acid probes (see page 429-430 bridging para; probe to 3' downstream region of Myf-3) to determine the methylation state of genomic CpG sequence for Myf-3. Iacopetta teaches that hypermethylation of the Myf-3 gene is strongly associated with the development of benign and malignant colorectal tumors, therefore Iacopetta teaches "making a diagnostic or prognostic

prediction of the cancer based at least in part on the methylation state of the genomic CpG sequences (see page 431, col. 1, first sentence of "Discussion"). With regard to claim 18: the CpG sequences analyzed by Iacopetta 'correspond to CpG islands' which are 'associated' with sequences defined by SEQ ID NOS 7-9. It is noted that this recitation has been broadly interpreted to encompass the gene which is can be analyzed by the recited SEQ ID NOS in the claim. With regard to claim 19, the MYOD1 gene analyzed by Iacopetta is "defined by the oligonucleotide primers and probes" of SEQ IDNOS 7-9. It is noted that this recitation has been broadly interpreted to encompass the gene which is can be analyzed by the recited SEQ ID NOS in the claim. The claims do not require analysis with the specifically recited SEQ ID NOS:.

Iacopetta does not teach analysis of methylation alteration with DMH, however, Huang teaches the analysis of methylation status in nucleic acids using DMH, an array based analytical method that detects changes in methylation status based on arrays which comprise probes for screening methylation status of sequences (see abstract, page 468, col. 2). Huang teaches that the use of DMH allows for high density, DNA array based screening, and allows for more precise measurement of the frequencies and extent of methylation. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the analysis method used Iacopetta, with the DMH analysis of Huang. The ordinary artisan would have been motivated to improve the methylation analysis of Iacopetta, because Huang teaches that analysis with DMH allowed for more precise measurement of the frequencies and extent of methylation. The ordinary artisan would have had a reasonable expectation of success that the DMH analysis method of Huang could be used instead of the analysis method

used by Iacopetta because Huang teaches of successfully determining alterations in methylation patterns of nucleic acid in breast cancer analysis.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. It is noted that the amendment submitted 5/16/2005 lists the status identifiers for claims 21-24 as original. While these are original claims, they are also withdrawn. The withdrawn status of the claims should be included in any subsequent submission of such claims.

13. No claims are allowable.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-

0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jehanne Sitton

Jehanne Sitton
Primary Examiner
Art Unit 1634
8/8/05